IRB ADVISOR

Your Practical Guide To Institutional Review Board Management

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Central IRBs: Consistency increases, but so does confusion

Pros and cons are weighed

As the use of central IRBs grows nationally, these models are increasing consistency in IRB review, but they also are causing some confusion for institutional IRBs, research ethics and IRB directors say.

"Centralized IRB models can increase the consistency of human subject protection," says **James Riddle**, MCSE, CIP, CPIA, assistant director of Fred Hutchinson Cancer Research Center in Seattle.

"Having one location where the research is consistently reviewed helps ensure consistent protections apply across all of the institutions doing the protocol," he adds.

Research institutions increasingly are awarded federal grants that require a centralized IRB model out of a desire for greater consistency, Riddle says.

One of the driving forces behind the centralized IRB model was the perceived lack of IRB review consistency between sites reviewing the same multisite study. But now that centralized models have become more accepted and consistency is improving, a new administrative problem has arisen, Riddle says.

In recent years, research institutions working with central IRBs have discovered that the efficiencies gained from having a multisite study use one main IRB have not trickled down to the local IRBs.

"Just because you're using a central IRB doesn't mean it's less work for the IRB office," Riddle says.

"You still have to keep track of the central IRB and what the rules are," Riddle says. "So you might improve study time and efficiency of the overall IRB system, but you may also end up adding administrative burden to keep track of all of those different centralized IRBs and their unique requirements."

For larger research institutions like Fred Hutchinson Cancer Research Center, there often are three or more central IRBs being used at one time,

Riddle says. *(See story about different central IRB models, page 112.)*

"Each institution has to come up with their own mechanisms for working with central IRBs," he says.

The human subjects protection world is in transition with centralized IRBs, and while this makes things more confusing, it will evolve and improve, says **Kathryn Flynn**, PhD, an associate professor at the Medical College of Wisconsin in Milwaukee. Flynn has studied the central IRB model and published research about it.

"Right now, in this transition period, it might mean extra paperwork for IRBs, but hopefully this is only for the transition period," Flynn adds.

The ideal is for both local and central IRBs to agree on terms and a workable model, she says.

When the first centralized IRBs emerged in the 2000s, institutions and local IRBs were concerned about whether involvement of central IRBs would affect the local and institutional IRBs' ability to reflect community standards, but this has not proven to be a problem, says **Robert Klitzman**, MD, professor of psychiatry and director of the bioethics masters and online certificate programs at Columbia University in New York City.

"Centralization has a lot of advantages, and what I've found in research is that there are several advantages to having local IRBs, as well," Klitzman says. "One advantage is that local IRBs have local knowledge of subjects and researchers."

For instance, members of a local IRB might have a curbside consult with investigators, he says.

"An investigator might see an IRB member in the parking lot or hallway and say, 'I'm thinking about doing this with my study, what do you think?'" Klitzman says. "The IRB member might answer, 'Make sure you're aware of XYZ.'"

The researcher takes that informal advice and incorporates changes in the protocol before sending it to the IRB for review. That informal process can save a month or more of IRB review time and back-and-forth between investigators and the IRB, Klitzman explains.

"A parking lot is not a place for an official decision, but any informal network can be helpful," he adds.

The research community can do more to improve local IRB and central IRB relationships and to increase efficiency when centralized IRBs are used, Flynn says.

Flynn was the lead author of a study that looked at perceived barriers to using centralized IRB review and discussed the need to clarify terms.[1]

"Ten years ago there was a conference that outlined main barriers to centralized IRB review, and we were trying to present some potential solutions to these barriers," Flynn says. "We talked with a number of different stakeholders, received their feedback, and presented solutions to barriers."

Flynn and co-investigators spoke with more than 40 experts, including IRB directors, federal regulators, and others.

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Editorial Questions

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"We held a two-day expert meeting to get all of these different perspectives," Flynn says.

One barrier identified was the feasibility of working with multiple outside IRBs when each required different forms. The solution Flynn and co-investigators suggested was for the research community to identify standard data elements to facilitate review and reporting across disparate systems.[1] *(See story about IRB responsibilities on this page.)*

The centralized IRB model still is new, so it's too soon to say whether it's the best model for human subjects research review, Flynn says.

"Theoretically it looks like it should be the better model, but it remains to be seen," she adds.

When research institutions form a partnership with a central IRB, the human subjects protection community should be cautious of expecting too many benefits from this relationship, Klitzman says.

"The problem is that people are looking to central IRBs to solve significant discrepancies in IRBs' decision-making," he notes.

But a central IRB is not the answer to all IRB standardization problems, he adds.

Klitzman's research has shown that discrepancies in IRB reviews can occur within a local institution and even within a single IRB, as well as between IRBs that are entirely different. This suggests that most IRB review inconsistency is due more to individual board members' opinions than to differences in community standards, as is usually suggested, Klitzman says.[2]

IRB review is a human process, and this makes consistency more challenging, he says.

While CITI and other human subjects training are widely used by researchers, clinical trial staff, and IRB workers, such training is rarely required of actual IRB members, Klitzman says.

"Why isn't there a required test to be an IRB member?" he says. "If researchers have to take a test, IRB members should take a test."

The field's dilemma is similar to that of psychiatric research 30 years ago, when one psychiatrist would say a patient is depressed, but another would think that was overstating the problem, he explains.

"So the psychiatric field developed standardized rating scales that tell us if someone is depressed or not," Klitzman says.

The same sort of rating scales could be developed for the IRB process, he adds.

"What we need is open, transparent discourse," Klitzman says. "It's in the absence of this that people believe central IRBs are the answer."

Making the IRB process more consistent would require both a checklist that IRB staff can use to make certain each submitted study follows all regulations, and a review rating scale to look at issues where personal opinions can sway a decision one way or the other, he says.

An IRB review rating scale could look at the informed consent process, the concept of undue influence, the balance of risks and benefits, and other issues.

"I would argue it's still a human process and we can't automatize everything, but there needs to be much more of an attempt to do so," Klitzman says. "The differences between IRB reviews are not related to community values but are due to idiosyncrasies, and that's an unacceptable reason for inconsistency."

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Dividing central and local IRB responsibilities

Researchers offer suggestions

When research institutions and their IRBs work with centralized IRBs, questions arise about which board handles which responsibilities.

Researchers with the Clinical Trials Transformation Initiative (CTTI) took a close look at this, coming up with a study that suggests these common roles for central IRBs:

- research education and training of IRB personnel;
- register with FDA and OHRP;
- notify sites of accreditation changes;
- ensure ethical standards and regulations;
- collate site-specific information;
- approve informed consent forms;
- provide copies of IRB decisions, rosters and minutes; and
- notify sites of non-compliance concerns.[1]

Suggested responsibilities for local IRBs include the following:

- education and training of investigators and study coordinators;

• credentialing of staff;
• maintaining Federalwide Assurance (FWA);
• conducting security and privacy reviews; and
• ensuring investigator compliance and conflict of interest.[1]

Either IRB could evaluate local context or provide waiver of authorization under HIPAA, and both IRBs could execute IRB authorization and assess investigator qualifications.[1]

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1. Flynn KE, Hahn CL, Kramer JM, et al. Using central IRBs for multicenter clinical trials in the United States. *PLoS One*. 2013:Jan. 30, 2013. ■

Examples of central IRB models

IRBs could be working with any and all

Working with different central IRBs and using different models has created some confusion for local IRBs, experts say.

Each central IRB has its own model for working with local ethics boards, says **James Riddle**, MCSE, CIP, CPIA, assistant director of Fred Hutchinson Cancer Research Center in Seattle.

For instance, a research institution might be working with central IRBs that have one of these different models:

• **Shared model.** "Most institution-based IRBs don't have the resources to provide all of the same resources as a commercial central IRB, so some of the responsibility is shared," Riddle says.

An example is the Central IRB (CIRB) Initiative formed by the National Cancer Institute. CIRB performs protocol review, amendments, and continuing review, but there also is work done by the local institutional IRB, including preparation of the final informed consent form, Riddle says.

Another shared IRB model, called IRBShare, is where one institution will provide the initial review of a research project. Then other institutions participating in the IRBShare project can rely on the first institution's review of the protocol as their own, he explains.

"That model, essentially, is sharing the initial review responsibilities, but after the initial review, each institution then conducts local review of amendments, continuing review, reportable events, etc.," he adds.

• **Optional lead IRB model.** "When Fred Hutchinson serves as the central IRB, we use a model we call the lead IRB," Riddle says. "We use this model for various research networks where Fred Hutchinson is the network coordinating center."

It provides centralized IRB services on a voluntary basis to members of the network. The chief example of this model is the Cancer Immunotherapy Trials Network (CITN), which is located at Fred Hutchinson.

"We are the coordinating center, and all of the participating network sites are offered the opportunity to use the Fred Hutchinson IRB as the IRB of record, or they can use their own local, institutional IRB," Riddle explains. "It's an optional, centralized IRB — not required."

About half of the CITN sites use Fred Hutchinson IRB as their central IRB, he adds.

With the lead IRB model, the central IRB does all of the IRB-related work, including initial review, modifications, and unanticipated problems reporting. The local IRB does its regular institutional activities, including handling conflicts of interest, Riddle says.

• **Mandatory central IRB model.** Some federal research grants have required the receiving institution to provide compulsory central IRB review. The compulsory use of central IRBs may become more prevalent as funding agencies require all participating sites to use the central IRB as a condition of the research grant, Riddle says.

"Those are just three examples of central IRB models," he says. "There probably are dozens more that have been springing up as NIH [National Institutes of Health] and other funding agencies have mandated the use of a centralized IRB system." ■

One-page form aids in serious event reporting

Questions should go into gray areas

How investigators report serious adverse events (SAEs) can be subject to gray zones. Answers are not always a clear "yes" or "no."

For this reason, an IRB should have an SAE report form available to help clarify investigators' responses, suggests **Brian A. Gladue**, PhD, CIP, executive director for the office of research

compliance at the University of North Texas Health Science Center in Fort Worth.

"The investigator has to determine whether or not the event meets one of the standard criteria for serious adverse event, such as death, life-threatening situation, hospitalization," Gladue says. "And how is the event related to the protocol?"

An SAE report form should allow for a small range of answers, he says.

"It encourages more reporting if the answers are not just 'yes' or 'no,'" Gladue says. "We find that people are reluctant to say 'yes' or 'no.' So having a range gives them an opportunity to check something."

But if the investigator answers with anything other than a definite "no," the IRB will look into it, he adds.

"If the investigator is convinced the event is not related to the protocol and their explanation makes sense, then we'd concur," Gladue says.

The IRB provides investigators with an SAE checklist to get them to think about the kind of information the IRB needs, he says.

"Then they attach all of the relevant data, usually as it relates to the study," he adds. "We ask for what the determinations are and what they recommend."

The IRB reviews the SAE information and decides to accept it as-is or to modify the informed consent form.

The attached information should include a description of what happened, any available medical or hospital record and diagnostic record associated with the event, and lab tests associated with the event, Gladue says.

"The form is a starting point, not a single, end-all document," he explains. "They have to attach relevant information, and if this is not forthcoming the IRB will ask them for more information."

For example, the SAE report also should include the investigator's determination of the event and how it's related to the kind of event they're reporting, Gladue says.

"Some events are clearly related to the study, and some are unrelated, or you have to stretch it to have it related," he says.

Gladue offers this example of how gray areas can develop: "Suppose someone is taking a test article associated with diabetic foot ulcers, a cream or treatment, and the person ends up in the emergency room over the weekend because he broke his shoulder when cleaning gutters."

The investigator might say this accident is definitely not related to the study. But someone else might argue that the participant could have been woozy from the study product and that could have contributed to his fall, Gladue explains.

"So the IRB will look at the test article's adverse events to see if wooziness is listed," he says.

Any adverse events result in a reassessment of what's going on with the study.

"The idea is to have a system available for investigators to be comfortable about reporting unusual events that occur in their protocols, and the SAE form is the starting point for that," Gladue says. ■

New president and CEO: "We're AAHRPP '2.0'"

Paperless submissions started in April

The Association for the Accreditation of Human Research Protection Programs (AAHRPP) is moving in some new directions as **Elyse I. Summers,** JD, president and chief executive officer, celebrates her first anniversary with the organization. Summers previously was the director of education at the Office for Human Research Protections (OHRP). *IRB Advisor* asked Summers to answer a couple of questions about AAHRPP changes under her watch.

***IRB Advisor*:** What are some of the new things AAHRPP is doing?

Summers: We're really focusing on working collaboratively with and listening to our various stakeholders so as to make the whole accreditation process as positive of an experience as possible for all concerned. For example, we have all of our AAHRPP standards that organizations do need to meet, but I've articulated as an operating principle that in areas where the regulating agencies — whether it's the FDA or OHRP — have put forth regulations and guidance and clear interpretations, AAHRPP does not need to be "greater than." AAHRPP will not create greater standards than what has already been fully and well explicated by the regulatory agencies.

Alternatively, there may be areas where there are regulations but not guidance or explicit interpretations from the regulatory agencies, and

in those areas we have stepped into the void to help illuminate what needs to be addressed. If there's a gray area where the community was seeking some guidance, we have stepped in and provided further elucidation in those areas. For example, there are regulations that describe the IRB's structure and composition, including the necessity of having experienced IRB members and a designated IRB chair, but AAHRPP standards (II.1.B) provide for periodic review and adjustment, as necessary. In other words, IRB members (and chairs) should be evaluated and given feedback in terms of their participation.

A second example (standard II.1.C) involves managing the potential for conflicts of interest between different role-players at an organization. AAHRPP standards require that an organization have and follow written policies and procedures to separate competing business interests from ethics review functions, such that, for example, the person in charge of attracting grant money cannot be the IRB chair. Those are competing interests: The IRB chair has to say whether or not the study is ethically appropriate, and the grants director needs to attract research funding. While I'm fairly confident that my former colleagues at OHRP would recommend such separation of function to maintain the IRB's independence, on this specific issue the regulations are silent.

Returning to my earlier point, I want to be clear, though, that one of the things I'm trying to counter is the possible perception in the community that AAHRPP requires more than federal agencies in areas where the government has spoken quite cogently, robustly and appropriately; in those cases, we do not require more. For instance, in the case of continuing review, there is well-explicated harmonized guidance from OHRP and FDA, so that is a situation where there is no reason for AAHRPP to require greater than what the regulations require because the federal regulators have spoken in a clear and helpful manner.

***IRB Advisor*:** What is AAHRPP doing differently now?

Summers: We're trying to make strides in the functional processes of accreditation. Before I started at AAHRPP, everything had to be submitted in physical hard copy paper — hundreds of pages. Now we're working towards a paperless process. Although we're not fully there yet, we have begun to accept our submissions by CD or thumb drive. It's not the same as a fully online portal yet, but we want to do that carefully. We're on our way to implementing processes that make the whole experience a better one for our clients. We changed this just this past spring. If an organization wishes to send paper, we'll accept that, of course, but this is huge because the submission process includes hundreds and hundreds of pages. This change saves trees and the expense of mailing and express delivering things to us. It's worked great. The organizations like it and our staff loves it.

The main notion we've been trying to put out there is we're AAHRPP 2.0 now. AAHRPP's founding president, Marjorie Speers, did an incredible job of getting AAHRPP off the ground and developing this great organization dedicated to recognizing and accrediting high-quality human research protection programs. And now we're moving into our second phase of existence, looking for ways to both reconnect with our founding community as well as areas where we can grow and be innovative and helpful to our community. ■

The changing world of independent IRBs

Acquisitions mean big changes, more services

Thanks to the rise in private equity ownership, the number of independent IRBs may be shrinking, but the number of services they offer is greatly expanding.

To get a sense of what is changing in the independent IRB field and why, *IRB Advisor* spoke to current and former CEOs of Schulman Associates IRB, WIRB-Copernicus Group, and Chesapeake IRB.

While independent, medical, and academic IRBs are all driven by the same goals — ethical research and the protection of human subjects — independent IRBs must also consider what other IRBs may not have to: the business of staying competitive and just staying in business.

"Right now you really only see four major IRBs: WCG [WIRB-Copernicus Group], Schulman, Quorum IRB [family owned], and Chesapeake," says **John Isidor**, JD, CEO of Human Subjects Protection Consulting in Cincinnati, and former CEO of Schulman Associates. "The

family-owned nature of the IRBs is dying rather quickly with the private equity firms entering."

"As far at the notion of consolidation — an industry doesn't consolidate on its own," says **Don Deieso**, PhD, CEO of WIRB-Copernicus Group (WCG). "It usually happens because the market is savoring that. We didn't set out as a company to consolidate an industry."

Expanding services

One big reason behind the IRB acquisitions, Isidor says, is that IRBs are looking to expand their service offerings.

"Pre-2007, I don't think any IRB did anything other than act as an IRB," he says. "Our entire focus was on improving turnaround times and customer service and trying to get more specialized IRB members to make sure we had appropriate expertise reviewing the research."

One example of expanding services is Schulman's recent foray into consulting with its formation of Provision Research Compliance Services. The partnership between Schulman and Falcon Consulting Group provides quality assurance and human subjects protection consulting services.

"That was really an effort on our part to broaden our service lines to better reach the compliance needs within institutions," says **Michael Woods**, CEO of Schulman Associates IRB in Cincinnati. Schulman was purchased by Imperial Capital Group in 2008. "We wanted to be able to do more than simple review services, and provide support to the human research protections programs within institutions and ensure the compliance of the enterprise." Both Schulman and Falcon wanted to expand their service offerings, Woods says.

To expand its service offerings to clinical research organizations and other institutions, WCG offers an institutional biosafety committee for gene transfer and recombinant DNA trials. The company also acquired tech company IRBNet, which provides IRB and clinical trial management software.

"There's been a resounding market acceptance," Deieso says. "One of the advantages of being a larger organization is that you can invest more."

The bottom line, Isidor says, is that private equity firms buy to sell. Firms look at how to grow the top and bottom lines of the entity they wish to purchase. "The model for the independent IRB is not perfectly aligned with the private equity model because there isn't an unlimited amount of growth there," he says. "If anything, it's either flat or somewhat reduced because of costs and patients that are accessible."

The IRBs' focus on human subjects protection must remain firmly intact, Isidor says. "These private equity firms are well aware that if they do things to raise revenue and speed studies along, that could be the death knell of the IRBs," he says. "I think they're certainly aware that they can't push the envelope too far — they understand the impact of the FDA, OHRP, AAHRPP, and the ethical nature of what the companies do."

Working with private equity can increase risk awareness even more, Woods says. "Our experience with private equity has heightened our focus on doing everything we can to ensure a very compliant, high-quality service," he says. "I believe in the world of private equity, they're looking to achieve certain business objectives and they need to do that in a way that minimizes risk as much as possible. Risk is something they have very little appetite for."

Grow or bust

The IRBs became aware that they would almost certainly have to sell in order to grow technological offerings and stay competitive, the CEOs acknowledge.

"Obviously the other aspect we were all competing on was electronic tools to let customers access data in a time-sensitive manner," Isidor says. "One other area for growth was offering services to larger institutions that would use independent IRB services or primarily commercial-sponsored research."

"I think it's the reality that they [smaller independent IRBs] can no longer satisfy the market needs," Deieso adds. "They can't go it alone anymore. If you don't have the technology to live in a paperless world, customers won't use you anymore and will find a better option."

"Part of the decision on my part [to sell] was to be a competitive player in the field while maintaining the high level of quality that we provide," says **Felix Khin-Maung-Gyi**, PharmD, MBA, CIP, RAC, founder of Chesapeake IRB and and executive chairman of Chesapeake Research Review, LLC, in Columbia, MD.

Resources are scarce for personnel and other funding needs, Gyi says, and IRBs must have certain economies of scale. This includes efficient

technology platforms that are easily accessible to clients and facilitate timely research. "If an IRB hopes to be able to provide that type of support and they have not yet invested in the electronic infrastructure, it will be an expensive and difficult initiative to undertake today," he says.

Chesapeake invested in a Part 11 compliant electronic platform in 2005, which it continues to expand and improve. The capital from Audax Private Equity allows it to improve technology that supports the growth the IRB is currently experiencing, Gyi says. "I don't see how we, as a research enterprise, can afford not to be efficient if we are to remain a viable provider of services," he says.

Multisite research

The growing use of central IRBs for multisite research is driving consolidation, Gyi says. "Enlightened sponsors, researchers and academic centers see the world is changing — consolidation supports timely intiation of multisite studies," he says. "There have been many models suggested; in the early 2000s, the question was, 'How can we run a more efficient multicenter trial so 100 different research sites don't have to answer to 100 different IRBs?' You don't want to have 100 different interpretations resulting from the review of the same protocol. It's been a topic that's been underlying many conversations in the field. It's now percolating to the top and people are seeing that they can indeed have one IRB that provides oversight that's in compliance with regulations and ethical considerations. The profile of multicenter studies hasn't really changed; what has changed is how a central review model can be a tremendous benefit in conducting multicenter research. This is further evidenced by academic medical centers relying more and more on central IRBs like Chesapeake's to provide human research protections oversight for their investigators."

"One other area for growth was offering services to larger institutions that would use independent IRB services for primarily commercial-sponsored research," Isidor adds. "The push continues to be spearheaded in part by FDA and OHRP for one central IRB for large and medium clinical trials. It offers a great advantage of marketing your IRB services to the client."

As the model and role of central IRBs continues to take shape, independent IRBs must find their role within the model, Gyi says.

"We have to elevate our conversation: What does central review model look like? What does the professional IRB look like in the central model?" Gyi says. "In those terms, the role of the independent IRB would grow because they have the infrastructure to be efficient in a quality multicenter research setting."

The future of independents

"The landscape is changing across the entire research enterprise, not just independent IRBs," Gyi says. "From pharmaceutical companies to academic medical centers to hospital consortia, there are governance and structural changes that affect how research is being conducted across the board. We all have to be more efficient, and have the capacity to be scalable, if we are to remain competitive globally — not just nationally."

The CEOs acknowledge that the trend of independent IRB acquisitions is likely to continue. "These acquisitions have certainly affected the model, and it appears at some point there will probably be very few, very large independents dominating the market," Isidor says.

"Other than just reducing the number of major IRBs out there, it has been a way to accelerate our growth and do in a couple of years what would have taken four or five years to do," Woods says. "It remains to be seen what the impact will be on the rest of the industry."

"If the market didn't favor fewer IRBs offering a wider array of services using more efficient technology, we wouldn't do it," Deieso adds. "It's the market that sets the requirements. The rest of us setting the market are the ones who perform. The smaller businesses will merge or go under." ■

Finding new capital partners

The stories behind the acquisitions

While consolidating the industry may not have been the goal of independent IRBs, the number of small and family owned IRBs continues to shrink.

Western IRB, Copernicus Group IRB, and IRBNet are all under the ownership of Arsenal Capital Partners. Aspire IRB, Midlands IRB and New England IRB are owned by the WIRB-Copernicus

Group (WCG). Just before this issue went to press, WCG announced the acquisition of New England IRB in Boston. Schulman Associates IRB in Cincinnati was sold to Imperial Capital Group in 2008. Audax Private Equity owns a majority stake in Chesapeake IRB, and just this year completed acquisitions of Cincinnati-based Goodwyn IRB and IRB Services in Canada.

When former Schulman Associates IRB CEO **John Isidor**, JD, and his partner decided to sell Schulman in 2008, they weren't necessarily looking to private equity firms. "Certain types of organizations [such as patient recruitment] were conflicted out of that process," he explains. "One IRB was interested, but it was mainly private equity firms. They had more of a neutral interest. We were pretty large, so it wasn't like another IRB would buy us."

Finding a partner with shared values and commitment to human subjects protection is key, says **Felix Khin-Maung-Gyi**, PharmD, MBA, CIP, RAC, founder of Chesapeake IRB and Executive Chairman of Chesapeake Research Review, LLC, in Columbia, MD.

"There has to be evidence of dedication to human research protections in an ethical way," he says. "We have to have shared values and demonstration of those values by having transparent and efficient infrastructure and procedures in place. Of course, a group that has growth potential is what attracts any buyer."

Several of the IRBs acquired by the firms have carried on with management structures and day-to-day operations intact. For example, Audax stays out of the daily operations of Chesapeake IRB, Gyi says.

"We have a tremendous partner in Audax. They leave the existing management structure intact and let the people who are growing the business do so and offer support and access to dollar and non-dollar resources as needed," he says. "They stay out of the way of the IRB's day-to-day business."

WIRB-Copernicus Group (WCG) and its member IRBs operate as separate entities, each with its own management structure. "We give them the resources, capital, technology, and support they need to flourish," says **Don Deieso**, PhD, chairman and CEO of WCG. "We haven't touched anything at WIRB, Copernicus, Aspire, or Midlands. One of the things we feel strongly about is that we don't acquire and then tear things apart. Nothing has essentially changed except they have access to the systems we're offering them." ■

A prescription for regulatory fatigue

Protocol navigation relieves the symptoms

IRB, FDA, IBC, RAC, DSMB — just a few of the alphabet soup organizations and regulatory body steps a researcher must go through to get a protocol written, reviewed, and approved. This can lead researchers to burnout dubbed by some at the National Institutes of Health (NIH) as "regulatory fatigue syndrome."

"There are many steps to getting it [protocol] through the regulatory process," says **Sara Albert**, MPH, protocol navigator at the National Institute of Allergy and Infectious Diseases (NIAID) at NIH in Bethesda, MD.

To help alleviate investigators' regulatory fatigue and get protocols through the intramural approval process at NIAID, the institute developed the Protocol Navigation/Protocol Development Program (PN/PDP). The program assists NIAID intramural researchers in navigating the cumbersome protocol approval process. The PN/PDP was developed five years ago in response to a survey on clinical research barriers, says **Tracey Miller**, RN, CCRP, PN/PDP manager at Clinical Research Directorate/Clinical Monitoring Research Program, Leidos Biomedical Research, Inc., Frederick National Laboratory for Cancer Research, Frederick, MD.

"IRBs are perceived as barriers, and researchers said there were not enough clinical research support services to get protocols up and running," she says. "The clinical director wanted to be proactive and to help intramural investigators develop clinical studies."

The PN/PDP tracked the development of an HIV vaccine clinical research protocol that worked its way through the program in 2013. The protocol required review and approval from a slew of regulatory bodies including the Food and Drug Administration (FDA), the NIAID IRB, a scientific review committee, Data and Safety Monitoring Board (DSMB), Institutional Biosafety Committee (IBC), and Recombinant DNA Advisory Committee (RAC). "This particular investigator [for the vaccine protocol] asked for help navigating through the offices needed," Miller says. "If you all work together, you can get something done in a relatively short amount of time, given the complexity."

When a researcher reaches out to the PN/PDP,

he or she is asked to provide a study concept and hypothesis, and a sit-down meeting is scheduled to review logistics and see what services are required. "Some people need help with aspects of protocol development, such as consent writing, while some need full-scale navigation through the whole process of development, review, and approval," Albert says. "We usually start setting up timelines and the goal for study start if there is something they need to keep in mind, such as budgeting or funding issues. We try to work out what the game plan is going to look like, what approvals they need, and other logistical steps in that timeline, such as target dates for scientific review and IRB meetings." They also discuss issues in the concept that will need further delineation in the protocol, such as identifying special populations, eligibility requirements, recruitment needs, sample collection and storage, and required oversight, such as monitoring and safety reporting. "I think it really helps if we have a good concept that's fleshed out. The IRB has several templates for protocols and our initial step is to put it in the appropriate template, based on study design," Miller says. "We work on filling in the holes of that template."

"The investigator is the driver of the whole process," Miller continues. "We are mini project managers for the protocol. If there's a contract that needs to be written, we engage that department and keep everyone on pace and push people along who need to be pushed."

The timeline milestones for the HIV vaccine protocol hinged on initial protocol document drafting and revisions after each of the previous reviews. The PN/PDP participated in biweekly meetings between the study team and the pharmaceutical company during protocol development to discuss the status of various reviews and ability to meet deadlines in order to keep moving forward.

The first milestone was the scientific review, which involved a team of investigators reviewing the protocol for scientific merit. Once the medical writer from the PN/PDP drafted the protocol, incorporating edits from all parties involved, the review occurred. The scientific reviewers addressed the stipulations in the protocol and approved it in February 2013.

Once final details of the protocol and consent were solidified, an IRB-required regulatory review of the protocol occurred about two weeks prior to the anticipated submission date to the IRB. Representatives from the regulatory, safety, and monitoring offices reviewed the protocol to ensure documents included sponsor-required information. "The medical monitor then issues a no regulatory concern email. The researcher has to have that in hand prior to [IRB] submission," Miller says. The NIAID IRB office has a Web-based submission system and PN/PDP staff assist investigators with filling out the application and uploading the documents to the system. "Once the IRB receives the completed application, the IRB staff administratively reviews the protocol and if there are issues or concerns they talk with us about it," Miller says.

The PN/PDP and the investigator submitted the vaccine protocol on schedule to the IRB two weeks before the meeting, with IRB stipulations given a week later. IRB discussions of the protocol focused on ethical use of a placebo, analytical treatment stop, and risk-benefit analysis. The PN/PDP assisted the investigator with responding to the stipulations and the final protocol was approved in May 2013, three months after completing scientific review.

When possible, the protocol was submitted for other reviews concurrently with IRB review to cut down on lag time between submissions, meeting dates, and approvals:

- **FDA:** The PN/PDP assisted in preparing the investigational new drug application and other necessary documents. The FDA determine it safe to proceed in May 2013.
- **IBC:** Pending RAC outcome, the committee approved the protocol with stipulations, in May 2013.
- **RAC:** The PN/PDP assisted with the RAC application, which was submitted in April. The committee provided written comments in advance of the public meeting held in June 2013. The committee provided additional recommendations at the meeting, and the protocol moved forward.
- **DSMB:** The board reviewed the protocol in May 2013 and in June, made recommendations allowing it to proceed.

Post-approval lessons

Metrics collected by the PN/PDP showed that the approval process took about seven months for the study, including five handoffs prior to scientific review and eight handoffs prior to IRB approval.

"We do collect a lot of metrics for the program and look at the stipulations received and try to avoid them in the future," Miller says. "We also try to eliminate redundancies in reviews. Navigated studies tend to run about a month faster than non-navigated studies."

"This protocol moved faster than most with these types of logistics involved," Albert adds. "There were a lot of people to appease in the process. It was definitely smoother and it finished as quickly as we could have gotten it done; RAC only meets quarterly, so we had no control over that."

The symptoms of regulatory fatigue syndrome may be unavoidable but were substantially decreased for the investigator as a result of interactions and communications with the PN/PDP, Albert says. "The time lines helped the investigator manage expectations and set up a game plan early on and keep the stakeholders engaged and on track so that this would move along," she says.

IRB takeaways

The NIAID IRB has also benefitted from the PN/PDP, Miller says, and even refers investigators to the program.

"That has been very key to our success — they [IRB] say it's so much easier to read the consent documents and protocols and they know all the I's will be dotted and T's crossed," Miller says. "If the protocol hasn't gone through our process, the IRB might stipulate to seek out the services of the PN/PDP to condense or rework the wording or help with stipulation responses. Our IRB chair does seek out our service for his studies."

Elements of the PN/PDP program are adaptable to other research programs, Miller says. "There are elements that are unique to us, but quite a lot of people have been curious about our program and how they can help investigators because they hear the same complaints about inefficiencies and the onerous approval processes," she says. "Since we all have the same goal of getting protocols up and running, they [other IRBs] could take pieces of the program to fit with their own institutions." ■

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CNE/CME OBJECTIVES & INSTRUCTIONS

The CNE/CME objectives for *IRB Advisor* are to help physicians and nurses be able to:

- establish clinical trial programs using accepted ethical principles for human subject protection;
- apply the mandated regulatory safeguards for patient recruitment, follow-up and reporting of findings for human subject research;
- comply with the necessary educational requirements regarding informed consent and human subject research.

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COMING IN FUTURE MONTHS

- Evaluating informed consent requirements
- Biobanking IC consensus guidelines
- Ethical questions raised by strategies to retain participants
- Handling conflicts of interest

CNE/CME QUESTIONS

1. Which of the following is a role that could be performed by a central IRB, a local IRB , or both, according to a study co-authored by Kathryn Flynn, PhD?
A. Provide waiver of authorization under HIPAA
B. Execute IRB authorization
C. Assess investigator qualifications
D. All of the above

2. According to Brian Gladue, PhD, CIP, why is it a good idea for a serious adverse event form to allow for a small range of answers instead of just "yes"and "no?"
A. A range of answers provides an opportunity to score the answers, and IRBs can use the rating scale to determine their next action.
B. A "maybe" is a better answer according to OHRP regulations.
C. It encourages investigators to report more information while they might be reluctant to say a definite "yes" or "no."
D. All of the above

3. The Association for the Accreditation of Human Research Protection Programs (AAHRPP), under new leadership, is emphasizing which of the following:
A. AAHRPP will not create greater standards than what has already been fully and well explicated by the regulatory agencies.
B. AAHRPP will require IRB directors to hand-deliver applications.
C. AAHRPP will require at least one part of applications to include a video presentation of an actual informed consent session.
D. None of the above

4. According to the CEOs of independent IRBs, the need for new technology, expansion of IRB offerings, and an increased demand from contract research organizations (CROs) drive the IRB consolidations.
A. True
B. False